

US EPA ARCHIVE DOCUMENT



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

JAN 26 1983
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TO: Robert Taylor (25)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-767)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: EPA Reg.#201-279; 201-281; Bladex: Addendum to Rat
Teratology Study; PP#9F2232; Petition proposing a
tolerance of 0.1 ppm for the pesticide, 2-[[[4-
chloro-6-ethyl-amino)-5-triazin-2-yl]amino-2-methyl-
propionitrile, be established in or on Soybeans.
CASWELL#188C Accession#071285

Recommendations:

1. The requested action is not toxicologically supported.
2. The Bladex Fischer 344 rat teratology study needs to be repeated. Additionally, one other (rabbit) teratology study is also required to support the requested tolerance.
3. The incidences of anophthalmia, and anophthalmia and microphthalmia combined as well as diaphragmatic hernia in the Bladex study are still suggestive of a teratogenic effects. Conclusions relative to the teratogenic potential of Bladex will await review of the new studies.

Discussion:

1. Anophthalmia & Microphthalmia

In comparison to the fetal and litter incidences of anophthalmia, microphthalmia, and both of them combined in the Bladex teratology study, the Shell historical data shows that the fetal incidences of anophthalmia, and both anophthalmia and microphthalmia combined are much higher in the Bladex study than in Shell's historical control data as shown in Table 1. However,

the litter incidence of microphthalmia alone in the Bladex study (5%) is comparable to that found in Shell's historical data (5.1%). Shell's historical data is considered the most relevant historical data for comparison to findings in the Bladex study since the teratogenic evaluations were done at the same testing laboratory and appear consistent with other laboratory findings.

Considering the historical data from other laboratories, Dow showed a range of 0-0.5% and 0-0.83% for fetuses with anophthalmia and microphthalmia, respectively. The calculated mean percent incidence of these findings is 0.20 and 0.16, respectively, which is considerably lower than the results of the Bladex study and Shell's historical data. On a litter basis, the Dow data show a range of 0-5 for anophthalmia and 0-7.4 for microphthalmia which can be considered comparable with the mean values of Shell's historical data for microphthalmia and anophthalmia. However, the calculated mean percent of microphthalmia and anophthalmia from Dow's data on both a fetal and litter basis (0.20% and 0.16% for fetuses and 0.18% and 0.14% for litters) are considerably lower than the mean values in the Bladex study (4.12% and 1.03% for fetuses and 15% and 5% for litters) or Shell's historical data (0.39% and 0.49% for fetuses and 4.1% and 5.1% for litters).

The findings of the Wright-Patterson studies and the RTP studies are quite variable. The incidence of 14.81% litters affected with anophthalmia in the Wright-Patterson Study 1 is comparable to the results in the Bladex study (15%). Additionally, the incidence of microphthalmia in the RTP study (4.55% litters affected in studies 1 and 3) is comparable to the Bladex study. However, Wright Patterson study 1 had no microphthalmia and study 2 had no anophthalmia or microphthalmia. RTP study 2 had no anophthalmia or microphthalmia and study 3 had no anophthalmia.

Conclusions relative to the incidence of anophthalmia and microphthalmia in the Bladex study.

Relative to Shell historical data there is more than a 3 fold increase in incidence of anophthalmia in the Bladex study. It is the opinion of Toxicology Branch that conclusions should be based primarily on the comparison to historical data (unless questionable) from the same testing facility. Furthermore, neither the Dow nor the RTP data supported a 15% background incidence in this strain. Only a single study from Wright Patterson AFB had a similar incidence but use of this single study is not considered appropriate for comparative purposes. The 5% incidence

of microphthalmia occurring at the 25 mg/kg level in the Bladex study appears to be supportable as background incidence by the Shell and other historical data presented. However, if the combined incidence of both anophthalmia and microphthalmia is considered, an increase is still apparent in the Bladex study. Therefore, any final conclusions should await a repeat study.

2. Diaphragmatic Hernia

There appears to be a question regarding table #2 provided by the registrant. It is noted that at the 1.0 mg/kg dose level in the Bladex study that three fetuses with incomplete hernia and three fetuses with complete hernia add up to only four fetuses when combined (?).

Additionally, the litter incidence of 64% diaphragmatic hernia in Shell's historical data is much greater than the mean incidence of 24% in all groups of the Bladex study. However, neither the 64% litter incidence of diaphragmatic hernia in the Shell historical control data nor the 24% incidence in the Bladex study are reflected in the historical control data from other laboratories from which data was presented by the registrant or from any other reliable testing facilities. Dow Chemical Company reported a 0.34% mean for litters affected with diaphragmatic hernia. The historical data submitted from Research Triangle Park and Wright Patterson Air Force Base did not show any incidences of diaphragmatic hernia.

We must therefore conclude that both the Bladex study and the other Shell control data is seriously flawed. The Bladex study must be repeated.

Review:

1. Toxicology Data Submitted with this Petition.

a) Rat teratology study; Westhollow Research Center; (WRC RIR-180) Study #61230; 12/81; Additional historical data on Fischer 344 rats and Supplementary Information regarding Bladex Teratology Study (WRC RIR-180).

Summaries of the teratological findings of the Bladex rat teratology study and referenced historical data on Fischer 344 rats is shown below:

TABLE 1

INCIDENCE OF ANOPHTHALMIA AND MICROPTHALMIA IN FETUSES OF
BLADEX® TREATED AND HISTORICAL CONTROL FISCHER 344 RATS

Laboratory Anomalies	Fetuses Affected/ Fetuses Exam.	Percent Affected	Total		Percent Affected	Tab Number
			#Lit. Affected/ #Lit. Exam.	Percent Affected		
SHELL DEVELOP. (Dec. 1981)						
(Houston, TX)						1
Control						
Anophthalmia	0/82	0	0/20		0	
Microphthalmia	1/82	1.2	1/20		5	
Combined	1/82	1.2	1/20		5	
BLADEX 1,2.5 & 10 mg/kg						
Anophthalmia	0/259	0	0/56		0	
Microphthalmia	0/259	0	0/56		0	
BLADEX 25 mg/kg						
Anophthalmia	4/97	4.12	3/20		15	
Microphthalmia	1/97	1.03	1/20		5	
Combined	5/97	5.15	3/20		15	
SHELL DEVELOP. (August-October, 1982)						
(Houston, TX)						1
Anophthalmia	4/1025	0.39	4/98		4.1	
Microphthalmia	5/1025	0.49	5/98		5.1	
Combined	8/1025	0.78	7/98		7.1	
DOW CHEMICAL (1979-present)						
(Midland, MI)						2
Anophthalmia	5/2481	0.20 (0-0.5)	5/271		0.18 (0-5)	
Microphthalmia	4/2481	0.16 (0-0.83)	4/271		0.14 (0-7.4)	

Table 1: Continued

Laboratory Anomalies	Fetuses Affected/ Fetuses Exam.	Percent Affected	Total		Percent Affected	Tab Number
			#Lit. #Lit.	Affected/ Exam.		
WRIGHT PATTERSON (1978-1980)						
AIR FORCE BASE						
(Dayton, OH)						
Study 1						
Anophthalmia	7/181	3.87		4/27*	14.81	
Microphthalmia	0/181	0		0/27	0	
Study 2						
Anophthalmia	0/395	0		0/41	0	
Microphthalmia	0/395	0		0/41	0	
RESEARCH TRIANGLE INST. (1980-1981)						
(Res. Tr. Park, NC)						
Study 1						
Anophthalmia	1/178	0.56		1/22	4.55	
Microphthalmia	1/178	0.56		1/22	4.55	
Combined	2/178	1.12		2/22	9	
Study 2						
Anophthalmia	0/146	0		0/20	0	
Microphthalmia	0/146	0		0/20	0	
Study 3						
Anophthalmia	0/214	0		0/22	0	
Microphthalmia	0/214	0.47		1/22	4.55	

*Three fetuses in one litter and two fetuses in another litter.

TABLE 2

INCIDENCE OF DIAPHRAGMATIC HERNIA
 MEAN PERCENT AFFECTED (Number Affected)

Variable	BLADEX® Teratology Study (WRC RIR-180)					Shell Historical Data
	0	1	2.5	10	25	
Number of litters	20	19	19	18	20	98
Number of fetuses	82	76	93	90	97	1025
Incomplete hernia - Fetus	8.50 (5)	5.00 (3)	1.05 (1)	4.54 (4)	7.50 (7)	10.56 (102)
- Litter	20.00 (4)	15.79 (3)	5.26 (1)	16.66 (3)	20.00 (4)	63.27 (62)
Complete hernia - Fetus	0 (0)	5.00 (3)	1.05 (1)	2.78 (2)	3.00 (3)	0.56 (4)
- Litter	0 (0)	15.79 (3)	5.26 (1)	11.11 (2)	15.00 (3)	4.08 (4)
Combined - Fetus	8.5 (5)	6.3 (4)	2.1 (2)	7.3 (6)	10.5 (10)	11.11 (106)
- Litter	20.0 (4)	21.1 (4)	5.3 (1)	27.8 (5)	35.0 (7)	64.29 (63)

TABLE 3

DCM HISTORICAL CONTROL DATA (1979-Present)
FISCHER 344 RATS

Major External Alterations	Incidence of Fetal Alterations			% Fetus Affected ¹ Mean	Range	% Litters Affected ¹ Mean	Range
	External	Soft Tissue	Skeletal				
Number of Litters Examined	271	271	250				
Number of Fetuses Examined	2481	1322	2275				
Number of Control Groups	10	10	9				
	Total						
	#Fetuses Affected/ Fetuses Examined	#Litters Affected/ Litters Examined					
Amophtalmia	5/2481	5/271	0.22	0-0.50	2.03	0-5.00	
Microphthalmia	4/2481	4/271	0.17	0-0.83	1.54	0-7.41	
Diaphragmatic hernia	1/1322	1/271	0.04	0-0.43	0.34	0-3.45	

Conclusion:

The rat teratology study needs to be repeated. We will reserve our final determination regarding teratogenic potential until after we receive a repeat study (in Fischer 344 rats) and perform a thorough review.

Classification: Supplementary Data

William Dykstra *WDC*
1/26/83

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